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Fluorinated anti-tubulin phenyl-pyrroloquinolinones: *In vitro* and *in vivo* anticancer properties

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Tricycle Phenyl-Pyrroloquinolinones (PPyQs) are a class of compounds that have showed interesting *in vitro* and *in vivo* anti-proliferative activity acting as tubulin polymerization inhibitors by binding at the colchicine site into β-tubulin. The major initial focus on introducing fluorine into biologically active compounds is to improve their metabolic stability by blocking potential reactive positions with fluorine. In an attempt to reduce the oxidative metabolism of 7-PPyQs and at the same time to possibly maintain the excellent pharmacodynamic, we designed the synthesis of some compounds 12-15 and 19, monofluoro-phenyl derivatives of the earlier 3-ethyl-7-PPyQ 20 and 3-benzoyl-7-PPyQ 21. Of the new compounds synthesized, potent cytotoxicity (low and sub-nanomolar GI_{50} values) was observed with 12 and 13, both more potent than 20, in both leukemic and solid tumor cell lines. Neither compound 12 nor 13 induced significant cell death in normal human lymphocytes, suggesting that the compounds may be selectively active against cancer cells. In particular, 13 was a potent inducer of apoptosis in the A549 and HeLa cell lines. With both compounds, induction of apoptosis was associated with dissipation of the mitochondrial transmembrane potential and production of reactive oxygen species, indicating that cells followed the intrinsic pathway of apoptosis. Experiments carried out in a mouse syngeneic model demonstrated high antitumor activity of 13, which significantly reduced the tumor mass at doses four-ten times lower than that required for the CA-4P used as reference compound. Finally, molecular docking and metabolic stability studies of the newly synthesized compounds will be reported.

Biography

Matteo Dal Prà has completed his PhD at the University of Padova, School of Medicine, Department of Pharmaceutical and Pharmacological Sciences.

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